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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/537,859	03/28/2000	Paul Proost	49673	5520

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EXAMINER
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ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 03/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/537,859	PROOST ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 January 2002.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 13-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 13-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 March 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All   b) ☐ Some \* c) ☐ None of:  
1. ☒ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____       |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input checked="" type="checkbox"/> Other: <i>Sequence Notice to Comply</i> . |

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RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/15/02 (Paper No. 14), is acknowledged.
2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

*Misnumbered claims 15-25 been renumbered 13-23, and are referred to as such in this Office Action.*

Claims 1-12 have been cancelled.

Claims 13-23 have been added and are pending.

*Claims 13-23 are under consideration in the instant application.*

3. This Office Action will be in response to applicant's arguments, filed 1/15/02 (Paper No. 14). The rejections of record can be found in the previous Office Action (Paper No. 11).

It is noted that New Grounds of Rejection are set forth herein.

4. Applicant's cancellation of claims 1-4, 9 and 12 have obviated the previous objections and rejections with respect to these claims.

5. Sequence compliance: Applicant's provision of a CRF, Sequence Listing, and Statement that the contents are identical on 1/15/02 (Paper No. 14), is acknowledged. The CRF has been found acceptable and entered.

A) Applicant's provision of instant SEQ ID NO:2 (the mature MCP-2 protein of 76 amino acids) has provided a definite numbering system for the truncated forms of the "non-variant" MCP-2.

However, the changes made in this bona fide attempt to respond to the Notice of Comply that accompanied Paper No. 11 have now resulted in the omission of the MCP-2 full length sequence found in Figure 1 from the sequence listing.

**Therefore, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth above and on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.**

*It is suggested that Applicant amend the sequence presented under instant "SEQ ID NO:1" to provide the full length sequence of MCP-2 shown in Figure 1.*

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B) It is once again noted that there is a discrepancy in the sequence of the MCP-2 variant shown in Figure 1 in that it does not correspond to any sequence in the sequence listing. The MCP-2 variant sequence of Figure 1 differs from instant SEQ ID NO:3 at each of residues 67 and 69 (numbering according to the sequence listing). Instant SEQ ID NO:5, the truncated form of the variant MCP-2 sequence, also differs from the sequence of the MCP-2 variant of Figure 1 (i.e., residues 39 and 41 according to the numbering of the sequence listing are not found in Figure 1).

Applicant was previously requested to determine if the MCP-2 variant sequence of Figure 1 or the CRF is correct, and to *provide a clear explanation and documentary support for any requested alterations in the sequence listing or the drawings.*

If the sequence listing is in error, Applicant is reminded to provide a new CRF, Paper Copy of the Sequence Listing, and Statement that the CRF and Paper Copy are the same.

If Figure 1 includes an incorrect sequence of the variant form of MCP-2, Applicant is reminded to provide a proposed drawing correction or corrected drawings.

C) Finally, Applicant is required to identify the nucleotide and amino acid sequences with SEQ. ID NOS: wherever sequences occur in the specification and drawings in order to satisfy the requirements of 37 CFR 1.821 (d) (see also MPEP 2422.02-2422.03).

In particular, it is noted that *each of the two sequences presented in Figure 1 require reference to the appropriate SEQ ID NOS: (once provided), either in the Figure itself or in the Brief Description of the Drawings.*

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Application 97116863.8 filed in Europe on 9/29/97; application 97122471.2 filed in Europe on 12/19/97; and application 98104216.1 filed in Europe on 3/10/98 each appear to provide adequate written support for a truncated form of MCP-2 lacking residues 1-5 (that is, "MCP-2 (6-76)") and a mature MCP-2 protein comprising 76 amino acids ("MCP-2 (1-76)").

In addition, each of the priority documents appears to provide adequate written support for a MCP-2 protein missing "up to 5" amino terminal amino acids.

However, the phrase "up to 5" does not provide adequate written support for the instant language of "lacking NH<sub>2</sub>-terminal amino acids corresponding to amino acid residues 1, 1-2, 1-3, 1-4 or 1-5 of naturally-occurring MCP-2 (SEQ ID NO:2)". The instant claim language encompasses forms of MCP-2 that include NH<sub>2</sub>-terminal truncations of greater than 5 amino acids. As noted previously in Paper No. 11 and again below, the instant claim language can be interpreted to be drawn to any protein lacking these residues, regardless of whether or not additional residues are also missing.

Further, the "variant" MCP-2 sequences presented in SEQ ID NO:3, SEQ ID NO:5 and the lower sequence of Figure 1 do not appear to have support in any of the priority documents.

Thus the effective filing date of instant claims 13-14 and 16-23 is considered to be September 28, 1998, while instant claim 15 does appear to have an effective filing date of September 29, 1997.

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7. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. It is noted that required drawing changes are no longer being held in abeyance by the Office. Please see the form PTO-948 previously provided as part of Paper No. 11.

#### INFORMATION ON HOW TO EFFECT DRAWING CHANGES

##### A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

##### B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

#### Timing of Corrections

*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.*

8. 35 U.S.C. § 101 reads as follows:

*"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".*

9. Claims 13-16 and 21 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter, a product of nature.

The instant claims are drawn to an amino-terminally truncated MCP-2 lacking amino acids 1-5. The specification discloses on page 10 at lines 20-31 that MCP-2 lacking amino acids 1-5 compared to "authentic" MCP-2 is also produced by cells. Thus this truncated form of MCP-2 is a product of nature.

Applicant has argued with respect to similar claims in the response filed 1/15/02 that because the material is truncated, such material is not subject to a rejection under 35 USC 101.

However, as noted supra, the form of MCP-2 lacking residues 1-5 is produced naturally. The rejection is therefore maintained as it applies to the instant claims.

It is suggested that Applicant amend the claims to recite a "purified" protein, as disclosed on page 8 at lines 1-20. Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

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10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

11. Claims 13-14 and 16-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 13-14 and 17-23 are ambiguous in the recitation of "lacking ...residues 1, 1-2, 1-3 or 1-4", "lacks... residues 1-2", "lacks... residue 1", "lacks... residues 1-3", "lacks ...residues 1-4" and "lacks... residues 1-5".

As currently recited the meaning of these phrases is unclear. For example, the claims can be interpreted to be drawn to any protein lacking these residues, *regardless of whether or not additional residues are also missing*. Alternatively, the claims can be interpreted to be drawn to a protein lacking ONLY either residue 1, residues 1-2, etc.

Applicant's argument, filed 1/15/02, that the addition of a SEQ ID NO: obviated the rejection of record as it applies to the instant claims has been fully considered but has not been found persuasive essentially for the reasons of record in Paper No. 11.

Inclusion of a SEQ ID NO: by itself does not establish the metes and bounds of the instant claims when the ambiguity is associated with the number of amino acids lacking from the amino terminal.

B) Regarding claims 13-14 and 17-23, the phrase "naturally-occurring MCP-2 (SEQ ID NO:2)" renders the claim indefinite for at least two reasons.

As previously noted in Paper No. 11, the specification does not appear to provide a clear definition of the term "naturally-occurring MCP-2". Further, the specification indicates on page 10 at lines 20-31 that the form of MCP-2 lacking residues 1-5 compared to "authentic" MCP-2 is also a naturally occurring form. Therefore the term "naturally occurring MCP-2" is ambiguous as currently recited.

In addition, although Applicant has argued in the amendment filed 1/15/02 that the rejection of record would not apply to the instant claims because of the inclusion of a sequence identifier; the placement of SEQ ID NO:2 within parenthesis fails to establish the metes and bounds of the instant claims because it is unclear whether the limitation of SEQ ID NO:2 included in the parenthesis is part of the claimed invention. See MPEP § 2173.05(d).

It is suggested that Applicant amend the claims to recite "naturally-occurring MCP-2 consisting of SEQ ID NO:2", or to simply refer to the sequence identifier.

C) Claim 16 recites the limitation "has the amino acid sequence of SEQ ID NO:5". However, if claim 13, from which claim 16 depends is in fact limited to SEQ ID NO:2 (although as stated supra it is not clear if claim 13 is so limited), then there is insufficient antecedent basis for this limitation in claim 16. The amino acid sequence of SEQ ID NO:5 recited in claim 16 is not a truncation of SEQ ID NO:2 recited in independent claim 13, as discussed supra regarding sequence compliance.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.0.

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12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*

*(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.*

13. Claims 13-14 and 17-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Proost et al. (J. Immunol. April 1998; 160:4034-4041, of record, see entire document).

Applicant's arguments, filed 1/15/02 as they apply to the instant claims have been fully considered but have not been found convincing.

Applicant asserts that the instant claims have an effective filing date earlier than the publication date of Proost et al.

However, the priority date of the instantly rejected claims is considered to be September 28, 1998 for the reasons set forth supra in the discussion of Applicant's claim for foreign priority.

As previously noted, Proost et al. teach a naturally-occurring amino-terminally truncated MCP-2, lacking amino acids corresponding to amino acid residues 1-5 of full length MCP-2 (see entire document, e.g., Abstract or Discussion). Such a truncated form of MCP-2 would inherently possess the amino acid sequence of SEQ ID NO:2 which is lacking NH<sub>2</sub>-terminal amino acids 1-5. Proost et al. also teach that MCP-2 lacking amino-terminal amino acids 1-5 is an antagonist of other chemokines, especially MCP-3 (e.g. 2<sup>nd</sup> column of page 4038). In addition, although truncated MCP-2 in a pharmaceutically acceptable carrier is not explicitly taught, such a carrier is inherently present in the formulations of the protein used in the cell culture experiment of Figure 5.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced protein and compositions thereof.

The rejection is therefore maintained as it applies to the instantly pending claims.

14. Claims 13-14 and 17-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Rollins et al. (US Pat. No. 5,739,103, of record, see entire document).

Applicant's arguments, filed 1/15/02, have been fully considered but have not been found convincing.

Applicant argues that Rollins et al. is directed to truncations of MCP-1, and not MCP-2, because all of the Examples and the trust of the discussion of Rollin et al. is limited to MCP-1.

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However, as previously noted Rollins et al. teach and claim an amino-terminally truncations of chemokines including MCP-2 having antagonistic activity; and methods comprising administering amino-terminally truncated chemokines including MCP-2 (see entire document, especially columns 3 and 6-8 as well as the claims). The amino-terminally truncations taught by Rollins et al. include truncation of at least amino acids 1 and 2, since column 3 (as well as claims 5-7) teach that the truncation is to be "about 1 to about 10 or about 2 to about 7". As noted supra, the instant claims are not limited to truncations involving ONLY amino acids 1 or 1-2, 1-3, 1-4, or 1-5.

In addition, Rollins et al. teach recombinant production of amino-terminally truncated chemokines in eukaryotic cells, which would inherently result in a glycosylated protein (e.g., column 8, especially lines 11-20). Finally, Rollins et al. teach the formulation of the amino-terminally truncated chemokines including MCP-2 in a pharmaceutically acceptable carrier (e.g. columns 6-7); thus the limitation of a pharmaceutical composition comprising amino-terminally truncated MCP-2 is met.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced protein and compositions thereof.

The rejection is therefore maintained as it applies to the instant claims.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 13-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Damme et al. (J. Exp. Med. 1992;176:59-65, IDS #AM) in view of Gong et al. (J. Exp. Med. 1995;181:631-640, IDS AP), and in further view of Van Coillie et al. (Biochem Biophys. Res. Com. March 1997;231:726-730, IDS #AS).

Applicant's arguments, filed 1/15/02, have been fully considered but have not been found convincing.

Applicant asserts that it has not been established that Van Coillie et al. has a publication date before the priority date of the instant application.



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However, the copy of Van Coillie et al. provided as IDS reference #AX indicates that the reference was published in 1997 in the March 1<sup>st</sup> volume of Genomics. Thus Van Coillie et al. was published before the earliest effective filing date of any of the instant claims.

Applicant also argues that the rejection of record was based upon extrapolation of the cited documents without support for the extrapolation. This comment is addressed below in the context of the application of the rejection of record to the instantly pending claims.

The instant claims are drawn to amino-terminally truncated MCP-2, lacking NH2-terminal amino acids corresponding to amino acid residues 1, 1-2, 1-3, 1-4, or 1-5 and having antagonistic activity, and a pharmaceutical composition thereof.

Van Damme et al. teach the purification and characterization of MCP-2 as a C-C chemokine structurally and functionally homologous to MCP-1 and MCP-3 (see entire document). Van Damme et al. show that MCP-2, like MCP-1 and MCP-3, induces monocyte chemotaxis both *in vitro* and *in vivo* (e.g. pages 61-62).

Van Damme et al. do not teach amino terminally truncated MCP-2 that has chemokine antagonistic activity.

Gong et al. teach that amino-terminal truncations of the chemokine MCP-1 have chemokine antagonistic activity (see entire document, e.g., Abstract). In addition, Gong et al. teach a broadly applicable method of identifying chemokine antagonists by progressively shortening the amino terminus of MCP-1, then screening for receptor binding and inhibition of responses to the intact chemokine (see entire document, especially Figure 8 and Discussion). Gong et al. also teach that chemokine receptor antagonists can be used therapeutically to block monocyte infiltration, a key early factor in a number of allergic and chronic inflammatory diseases (summarized on page 631); and conclude that truncation of the amino terminus of MCP-1 provides a means for generating such antagonists (see concluding remarks on page 638).

Van Coillie et al. teach that there are two alleles of MCP-2 that differ at position 46: one allele encodes a Lys, while the other encodes a Gln (see entire document, especially the sequence of Figure 1). The difference between SEQ ID NO:4 and SEQ ID NO:5 of the instant claims is this allelic polymorphism.

Given the teachings of Van Damme et al. that MCP-2 is a structural and functional equivalent of MCP-1, the ordinary artisan at the time the invention was made would have been motivated to apply the approach used by Gong et al. to develop MCP-1 antagonists to also develop antagonistic amino terminal truncations of MCP-2. Since both MCP-2 and MCP-1 recruit monocytes which are important in a variety of inflammatory conditions; the ordinary artisan at the time the invention was made would have been motivated to produce and screen multiple amino-terminal truncations of MCP-2 in order to identify an antagonist of MCP-2 that could be substituted or combined with antagonists of MCP-1 to better inhibit monocyte recruitment in those inflammatory conditions.

The ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention by using the screening approach taught by Gong et al., including production of MCP-2 having the sequence of the SEQ ID NO:4 allele or the SEQ ID NO:5 allele. Further, the ordinary artisan would have been motivated to provide pharmaceutical compositions comprising any such antagonists in order to evaluate their relative efficacy in various disease models of inflammation; and would have had a reasonable expectation of successfully utilizing an MCP-2 antagonistic pharmaceutical compositions in inhibiting at least some models of inflammation. Finally, glycosylated forms of the amino-terminally truncated MCP-2 antagonistic proteins would be produced as a consequence of the expression systems that the ordinary artisan would utilize in order to produce sufficient quantities of the truncated MCP-2.

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Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as it applies to the instant claims.

17. No claim is allowed.

18. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
March 22, 2002

PHILLIP GAMBEL  
PHILLIP GAMBEL, PH.D.  
PRIMARY EXAMINER

TECH CENTER 1600  
3/25/02

<b>Notice to Comply</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	09/537,859		PROOST ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Jessica H. Roark		1644	

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
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